Can postoperative pain be predicted? New parameters; Analgesia nociception

Abstract

Background and Aim: The Analgesia Nociception Index (ANI) is a new method of identifying nociception-analgesia balance. In this study we investigate the correlation between the ANI / numeric rating scale (NRS) values immediately before-after extubation. NRS values recorded in the post-anesthesia care unit, in a group of patients who underwent a laparoscopic cholecystectomy, with the aim to evaluate the potential use of ANI values in the prediction of postoperative pain levels.

Materials and methods: The ANI and NRS values, the heartbeat rate (HR), systolic-diastolic arterial pressure (SAP/DAP) and oxygen saturation (SpO2) values of the patients were recorded into three groups based on the initial NRS values recorded at post anaesthesia care unit (group I: NRS ≤3, group II : NRS 4–6, group III : NRS ≥7). ANI value of lower than 47, (threshold value for pain) were recorded.

Results: Statistically significant increases were noted in HR, SAP and DAP after extubation, while there was no significant change in ANI values. A weak correlation was identified between the ANI and NRS values of all patient groups.

Conclusion: We failed to identify the correlation between ANI/NRS values before and after extubation. Previous studies suggest that ANI provides more valuable information in anesthetized patients, whereas our findings show that it is ineffective in the prediction of potential postoperative pain.

Keywords: General anesthesia, postoperative pain, intra/postoperative monitoring, analgesia nociception index (ANI)

1. Introduction
A pain-free life is one of the fundamental human rights, and controlling pain, particularly in the postoperative period, is of vital importance for patient comfort and the following recovery period. Almost 20–40 percent of patients suffer from severe postoperative pain that begins immediately after surgery [1]. Such severe pain occurs not only after long-lasting and complicated surgical operations, but may also be seen after several minor or moderate surgeries, such as tonsillectomy, hemorrhoidectomy, laparoscopic cholecystectomy and appendectomy [1].

The optimum method for assessing pain severity in post-anesthesia care units (PACU), where patients are monitored immediately after an operation, is still a matter of debate. In conscious and cooperative patients who came out of anesthesia, the commonly used assessment tools include the Visual Analogue Scale (VAS/0–100), the Verbal Rating Scale (VRS/1–5), and the Numerical Rating Scale (NRS/0–10) [2,3,4]. While VAS ≤30 and NRS ≤3 are considered as analgesia or tolerable pain, scores of VAS ≥70 and NRS ≥7 are considered to indicate severe pain [4]. There are, however, a large group of patients who are non-communicable (pediatrics, geriatrics, patients with communication disorders, unconscious patients, etc.) that face the risk of receiving insufficient pain treatment, despite all measures. Methods such as skin conductivity and pupillary reflex measurements have been tested in these patients to detect levels of pain [5-7].

In the recent years, the analgesia nociception index (ANI monitor / MetroDoloris Medical Systems, Lille, France), which assesses nociception-analgesia balance by measuring the parasympathetic system tonus, has emerged as a new method for the numerical and objective assessment of the sufficiency of perioperative analgesia [8,9]. ANI measures the duration between two R waves within heart rate variations (HVR) by filtering based on the variations in respiratory cycles, and provides a numeric measure of
parasympathetic tonus that varies between (p∑) 0 and 100. Based on this index, values of
50 and above indicate sufficient anesthesia, 30–50 indicate moderate pain, and values
lower than 30 indicate severe pain [9-12]. Over the last few years, researchers have
reported preliminary findings suggesting that the severity of potential postoperative pain
can be predicted objectively, irrespective of the physician’s subjective assessment, based
on ANI values recorded immediately after surgery [13], and this data may even allow the
prediction of the severity of early postoperative pain [14,15].

In the present study, we investigate whether or not a correlation exists between the ANI
values recorded at the completion of an operation, and immediately before and after
extubation, and NRS values recorded in the PACU in a group of patients who underwent
a laparoscopic cholecystectomy, and to evaluate the potential use of ANI values for the
prediction of postoperative pain levels.

2. Materials and methods

We gained approval for the study from the ethics committee (Istanbul Arel
University/69396709-050.01.01), to study with patients who provided informed consent
for the use of all their medical data in medical research, as long as their identity was kept
confidential. 36 patients who underwent laparoscopic cholecystectomies under
sevoflurane/remifentanil anesthesia at our hospital between May 1 and August 15, 2018,
who were monitored using the ANI and who were assessed for postoperative pain based
on NRS in PACU, were included in the study.

The study exclusion criteria included patients with ASA score other than ASA I – II, age
below 18 years or above 75 years, patients with an apparent cardiac disorder (primary
arrhythmia, ECG abnormalities, coronary ischemia, heart failure, etc.) and patients with
marked preoperative pain.
Additionally we excluded patients with an autonomous nervous system abnormality (epilepsy, previous CVE, etc.), those with chronic hypertensive patients taking beta-blockers, patients with a diagnosis of diabetes mellitus and patients who have been given ketamine, atropine, beta-blockers or another vasoactive substances at any time during surgery.

In order to minimize the potential difference in pain levels based on the surgical technique used, all surgical operations were performed by the same surgical team, where feasible. The routine general anesthesia protocol of our clinics for intraabdominal laparoscopic surgeries was followed for all patients who agreed to take part in the study. The monitoring procedures included a 5-electrode 2-channel ECG, oxygen saturation (SpO₂), noninvasive arterial blood pressure, end-tidal carbon-dioxide (ETCO₂), body temperature monitoring, and the recording of the analgesia-nociception index using an ANI monitor (ANI/MetroDoloris Medical Systems, Lille, France). As the only difference from the routine anesthetic protocol, spontaneous resolution of the neuromuscular blocker activity was awaited or a specific antidote (sugammadex) was administered to the patients in the study group during the postoperative period. In order to determine that neuromuscular activity was resolved spontaneously, we expected to observe that the patient had sufficient respiration, coughing and swallowing secretions. Additionally, the patient has to have eyes open, keep the head lifted for more than 5 seconds, keep the mouth firmly shut, and positively react to the tongue test. Sugammadex was used due to the decision of at least ten years experienced anesthesiologist to eliminate risks of residual muscle weakness that is a major risk for post-operative respiratory complications. The patients who were given an acetylcholinesterase inhibitor and/or anticholinergic due to a clinical need were excluded from the study. As is the case for all patients scheduled for surgery in our clinics,
the patients in study group were informed of the postoperative use of the numeric NRS and were explained how the postoperative pain evaluation would be made during preoperative visits, as per the routine clinical protocol. The premedication was performed by midazolam (0.03 mg/kg) and fentanyl (1 µgr/kg) in the operating room. Propofol (1.5 mg/kg) was used for anesthesia induction, orotracheal intubation and muscle relaxation were facilated by rocuronium bromide (0.6 mg/kg). 0.8–1.2 MAC sevoflurane, and air/O\textsubscript{2} mixture to maintain fiO\textsubscript{2} of 50 percent and remifentanil infusion (0.04 µg/kg/min) for analgesia were performed for anesthesia maintenance. Volume-control mode with 6–8 ml/kg tidal volume to maintain SpO\textsubscript{2} between 96–100% and E\textsubscript{2}CO\textsubscript{2} between 35-40%, was preferred for ventilation. If it is necessary, additional muscle relaxation by rocuronium bromide (0.15 mg/kg) was done. Our choice for perioperative fluid infusion was crystalloids (4 ml/kg/hour, unless there is an additional indication). Pneumoperitoneum was maintained by maximum carbon-dioxide gas insufflation pressure ≤15 mmHg. The body temperature was kept stable between 36.5–37.0 C° by intravenous fluids at body temperature, external heating during the perioperative period. Sugammadex (2–4 mg/kg) was used if clinically indicated that is to those patients that do not fulfill the above-mentioned criteria.

The ANI values of the patients, recorded immediately prior to extubation in the operating room and after extubation in PACU, and the pain scores based on a NRS within 10 minutes of the admission of the patients to the PACU, as well as the hemodynamics (Heart Beat Rate (HR), Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP) data and SpO\textsubscript{2} levels of the patients at the same time points were recorded. As per the clinical indication, patients with an NRS of >3 were given 1 mg/kg tramadol (30 minutes of slow
IV infusion in 100cc 5% dextrose) for postoperative analgesia. Patients who experienced no problems during routine monitoring were transferred to the surgery inpatient wards.

For data evaluation, patients were classified into 3 groups (group I - NRS≤3 (17 patients), group II - NRS 4-6 (11 patients), group III - NRS≥7 (8 patients)) according to the initial NRS values recorded at the PACU. The demographical parameters, duration of operation and ANI values were compared between the three groups. Patients whose ANI was lower than 47, considered as the pain threshold, and the groups these patients belonged to were recorded [13, 14]. Correlations between the ANI values recorded before extubation and at the time of coming out of anesthesia, immediately after the completion of surgery and after extubation in the PACU, and the NRS values recorded at the PACU were analyzed.

2.1. Statistical Analysis

Qualitative data was compared by using a Chi-square test, while quantitative data was compared between the groups using a student’s t-test for normally distributed parameters, and a Mann-Whitney U-test for non-normally distributed parameters. For within-group comparisons, a paired t-test was used for normally distributed parameters, and a Wilcoxon signed ranks test was used for non-normally distributed parameters. For all tests, p values of <0.05 were considered statistically significant, while p values of <0.001 were considered highly significant. Correlations between ANI values and NRS were investigated by a Pearson’s correlation test and “r” values were used to evaluate statistical significance. Based on these analyses, r values of 0.00–0.29 indicated weak, 0.30–0.49 indicated low, 0.50–0.69 indicated moderate, 0.70–0.89 indicated strong, and 0.90–1.00 indicated very strong correlations.

3. Results
A total of 36 ASA I-II patients, including 21 women and 15 men, were included in the study. The mean age of the study population was 45.33±12.43 years, and the mean body weight, height and BMI of patients was 74.22±12.64 kg, 167.55±7.72 cm and 26.21±4.49 kg/m$^2$, respectively. The average duration of operation was 68.41±15.81 minutes, and following the operation, the NRS values of the patients recorded in the PACU were ≤3 in 17 (47.22%) (Group I) and between 4 and 6 in 11 patients (30.56%) (Group II). NRS was ≥7 in eight patients (22.22%) (Group III). Table 1 summarizes the demographical findings, the duration of operation and NRS values in all groups. No significant difference was found between the demographic facts and ANI values.

During the stable phases of perioperative anesthesia, that is during the intraoperative period where only routine surgical and anesthetic procedures were applied without any unexpected events, the mean heartbeat rate (HR), SAP, DAP and ANI values of the patients was 65.31±16.76 beats/min, 95.67±15.06 mmHg, 59.72±12.34 mmHg, and 70.78±16.66, respectively. Before extubation, the mean HR, SAP and DAP increased to 70.44±15.42 beat/min, 111.97±18.89 mmHg and 71.44±14.39 mmHg, respectively, whereas the mean ANI decreased to 59.81±14.46. While there was a partial increase in hemodynamic parameters and a partial decrease in ANI, these differences were not statistically significant (p≥0.05). Following extubation, the mean HR, SAP, DAP increased but ANI decreased to 79.03±14.37 beat/min, 127.14±18.48 mmHg, 75.47±12.16 mmHg and 60.16±12.61, respectively. The increases in all three hemodynamic parameters were statistically significant (p<0.05). While there was a decrease in ANI, the difference was not statistically significant (p>0.05). Table 2 summarizes the findings.
Group I comprised a total of 17 patients (47.22%), including five ASA I and 12 ASA II patients whose postoperative NRS was \( \leq 3 \). The group was made up of seven women and 10 men, with a mean age of 45.41±11.53 years, a mean body weight of 74.41±12.12 kg, a mean height of 168.24±7.44 cm and a mean body mass index of 26.04±4.09 kg/m\(^2\). The mean duration of operation in this patient group was 67.26±11.56 min, and the mean ANI values recorded before and after extubation were 58.47±15.32 and 62.71±15.61, respectively. Group II consisted of 11 patients (30.56%), including seven women and four men, whose NRS was between 4 and 6. The mean age of these patients was 42.36±8.74 years, and nine patients were ASA I while the remaining two patients were ASA II. The mean body weight, height and BMI of patients in this group were 73.57±11.09 kg, 168.27±7.01 cm and 25.71±2.91 kg/m\(^2\), respectively. The mean duration of operation was 69.48±14.37 min and the mean ANI values recorded before and after extubation were 62.73±15.49 and 61.73±14.32, respectively. A total of eight patients (22.23%), including three ASA I, five ASA II, seven women and one man made up Group III with an NRS \( \geq 7 \). The mean age of the patients in this group was 47.87±14.94 years, their mean body weight, height and BMI were 78.21±11.82 kg, 165.13±9.41 cm and 27.34±3.39 kg/m\(^2\), respectively. The mean duration of operation was 68.45±13.76 min and the mean ANI values recorded before and after extubation were 58.50±15.16 and 55.13±13.54, respectively. While these values were numerically lower than in the other groups, the differences were not statistically significant (p \( \geq 0.05 \)). The other demographical findings, duration of operation and ANI values were also not significantly different between the three groups. In addition, the ANI measurements were lower than pain threshold level (47 for ANI) in six patients before extubation (two patients G I, one patient G II, three patients G III) and also they were lower in seven patients after extubation (four patients G I, one
patient G II, two patients G III). Only one patient who had an ANI value lower than 47 before extubation had a similar ANI value after extubation. All the relevant values are presented in Table 3. When post-extubation NRS-ANI correlations were investigated between the three groups, classified based on NRS values, the correlations with pre-extubation values were found to be “weak” for Group I (r= 0.016), “weak” for Group II (r= -0.286) and also “weak” for Group III (r= -0.293) which was the NRS ≥7 group. When the post-extubation ANI values were considered, the correlation coefficients indicated weak correlations for Group I (r= 0.135), Group II (r= -0.069) and Group III (r= -0.290).

The ANI and NRS values of the patients and the correlations between these values are presented in table 4 / figure 1 for pre-extubation, and in table 5 / figure 2 for the post-extubation time points, and figure 3 summarizes NRS-ANI distribution and correlation curves.

4. Discussion

ANI is commonly thought of as a numerical and objective indicator of perioperative analgesia levels [15], although some authors have suggested that potential hemodynamic changes can be predicted based on perioperatively monitored ANI values [16], while there have been further studies reporting the contrary [12,18,19]. Overall, almost all of those studies indicate that ANI values may be in line with clinical status, even during spontaneous respiration in sedated patients under the influence of anesthesia [17-19]. In addition, some studies tested the use of ANI to detect the level of analgesia in pediatric patients, and results of such preliminary studies were found to be positive [20,21].

Extending these general considerations, some authors argue that the severity of potential postoperative pain can be measured objectively based on ANI values recorded at the end of the perioperative period [13], and even that the level of pain can be predicted based on
these values, therefore allowing the early identification of severe pain risk and making
effective interventions accordingly [14,15].
In the present study, while 35.48 percent of the patients had mild pain that required no
analgesia, 64.52 percent required additional postoperative analgesics. Of all the patients,
22.23 percent had NRS ≥7, in other words, severe pain. This considerably high rate
detected during a relatively minimally invasive operation such as laparoscopic surgery is
proof of how important the concerns and actions to find a solution are. The rate identified
in this study is consistent with previously reported rates in literature [1].
In the present study, we failed to identify a correlation between ANI and postoperative
NRS, as suggested previously by some authors, and no significant correlation was noted
between the ANI values recorded before and after extubation and the NRS values in any
of our patient groups. In all patient groups, only a weak correlation was identified between
the ANI and NRS values. In addition, despite some limitations, our findings suggested
that ANI was ineffective in the prediction of potential postoperative pain, and these
findings are consistent with those of some other researchers [22,23].
The patient exclusion criteria used in this study resemble those used previously in almost
all studies into this issue, although there are some differences between these studies in
terms of the types of operation, the anesthesia protocols and the study design [23,24].
While ANI values recorded immediately before extubation were considered as the
measurement parameter in one of the first studies reporting a positive opinion on this
subject [14], another study took into account the ANI values recorded after extubation
[13]. In the present study, we investigated ANI values recorded at both time points, and
in this respect, we believe that our study is more inclusive.
In the present study, the ANI values recorded in the postoperative period immediately after extubation were found to be slightly lower than those recorded during the perioperative period. However, the difference between these values was not statistically significant. This can be easily attributed to the status of patients, who are still partially under the influence of anesthetic medications and who are gradually coming out of anesthesia and the effects of analgesic medications. There have also been several studies reporting that ANI values were markedly higher during deep sedation when compared to the awake periods, although this relationship is not proportional to the degree of sedation [22]. This is most probably true for our patient group too.

The ANI values also did not change significantly after extubation. In addition, the variations in ANI values were not parallel to the NRC values at either measurement time point. Low or high ANI values could be recorded in patients with apparent pain or in patients without any pain at all. In addition, aside from one patient, none of those who had an ANI value below 47 before extubation, and were theoretically assumed to have pain, had an ANI value below 47 threshold after extubation.

Other than pain, it is also possible that other factors which might affect the sympathetic nervous system, such as nausea, vomiting, agitation, anxiety, voice and others, may be involved and negatively affect the parameters measured at PACU. All of these factors may affect HR, and consequently, may influence ANI scores. Even the authors who suggested that ANI can be used for the prediction of postoperative pain underlined these potential effects [14]. In addition, there are authors who may be considered pioneers in supporting the use of ANI during the perioperative period also, who reported that the effectiveness of ANI is markedly decreased in conscious patients [17]. More recently, the results reported in two studies including healthy conscious subjects identified no direct
relationship between NRS and ANI, and highlighted the potential differences in individual responses [25,26]. In another study performed in 2015, Jess reported that ANI could not differentiate between painful, painless and fake stimuli in conscious subjects, and failed to detect nociception in conscious patients, while the values were affected by stress and emotional status. Based on all these findings, Jess at al. argued that ANI lacked the ability to assess pain severity in conscious and stressed individuals [25]. In 2017, Issa revealed a very weak negative correlation between ANI and NRS in healthy conscious individuals, and did not recommend the use of ANI in an emergency unit or intensive care setting [26]. Indeed, there have been some researchers who contributed to the development of ANI, such as De Jonckheere, that recently highlighted the relationship between ANI and emotional status, and even recommended use of ANI for the detection of parasympathetic changes in different emotional moods [27, 28]. Based on our findings, we also believe that ANI is better able to reflect pain under anesthetic conditions, whereas the values recorded after the patients come out of anesthesia are rather complicated due to the interactions between other confounding factors, and do not correctly reflect the balance between the sympathetic and parasympathetic nervous systems. On the other hand, we are currently engaged in further studies on ANI in different patient groups in our clinics.

Apart from all the above-described factors, ANI scores may also be affected by the applied anesthetic medication and the duration of exposure to such medications. While the mean duration of operation was approximately 65 minutes in all patient groups, the duration of operation in previous positive or negative studies varied between 30 and 180 minutes. Although there were studies that did not provide any clear data on this parameter, none of these studies considered the duration of operation to be a parameter with a direct
effect on the outcomes [29]. We believe that as duration of operation affects the total time
of exposure to anesthetic agents, and therefore, the total dose of analgesic medications, it
should be considered as making a considerable difference.

One of the reasons behind the conflicting results reported by previous studies may be the
differences in study designs. In the majority of studies reporting positive outcomes, total
intravenous anaesthesia (TIVA - propofol) was the preferred method of anesthesia, and
these studies have demonstrated that the performance of ANI was reported to be better in
studies using TIVA (propofol) than the studies using halogen-based agents [13,14,22,29].
Propofol and halogen-based agents have different effects on HR [30] and heart rate
control via the baro-reflex pathway [31]. While propofol decreases parasympathetic tonus
in parallel to the degree of hypnosis, halogen-based volatile anesthetics have no such
effects [32]. On the other hand, desflurane and isoflurane have been shown to decrease
neural system activity in total and to have a direct effect on sympathetic/parasympathetic
balance [33]. Moreover, there have been other studies demonstrating that, compared to
TIVA, high sympathetic activity that may affect HR and elevated plasma noradrenaline
levels can be seen after sevoflurane-based anesthesia [34]. Still, it is apparent that
halogen-based agents (sevoflorane, desflurane) are used much more often in daily
anesthesia practice when compared to TIVA. In the present study, sevoflurane was used
for the maintenance of anesthesia in all patients, and for this reason, we believe that our
anesthesia protocol more realistically reflects PACU conditions. Accordingly, we
conclude that the potential differences in the effects of the agents used for anesthesia
maintenance should be considered in future studies, and more importantly, addressed in
validation studies.
The types of narcotic agents used represent another difference in the study designs. Contextually, the differences of the opioids used to provide general anesthesia relate to their elimination half-lives. Nevertheless, almost all eventually have the same effects on HR. Narcotic agents inhibit sympathetic activity while preserving or increasing parasympathetic activity [35-38]. While Boselli et al. used remifentanil in both studies, demonstrating favorable findings [13,14], Ledowski et al. reported unfavorable results in his study using fentanyl as a narcotic agent [22]. It would appear, therefore, that it is more realistic to consider the preferred narcotic agent as having minimal effect on the outcome [29]. Our protocol also included the use of remifentanil, and the patients had completely overcome the effects of the applied narcotics at the time of admission to PACU, considering that they were given time to regain spontaneous respiration after the operation.

Indeed, other than anesthetic agents, there are several factors affecting HR at varying rates, although the effects of gender, age, awareness, varying hemodynamic and autonomic conditions, the percentage of inhaled oxygen, and the interactions between these parameters, are unclear [13,39,40,41]. Different classes of medications may also affect HR [42], among which acetylcholinesterase inhibitors used for the reversal of neuromuscular blockages and the anticholinergic agents used to prevent their cholinergic activity are of particular importance [43,44]. Although we excluded patients using medications affecting HR from the present study, and that we waited for the spontaneous resolution of neuromuscular blockage, or used a specific antagonist sugammadex in the presence of a clinical indication, we believe that our findings are not confounded by these factors. Accordingly, it can still be argued that ANI may not correctly reflect autonomous
system balance in routine use, given the common use of different medications with
different effects on HR in daily practice.

Generally speaking, these problems are not exclusive to ANI. When studies investigating
other methods of perioperative analgesia assessment, such as skin conductivity or surgical
stress index, are reviewed, it is apparent that the relationship between these alternative
methods with postoperative pain could not be proven for similar reasons [45].

It is necessary for us to underline some limitations of this study. Although the number of
patients included in this study was comparable to previous studies, it should still be kept
in mind that there were only a limited number of patients and no control group. Moreover,
all of the patients fell within a certain age interval, and included ASA I/II and relatively
healthy patients who were not receiving any concomitant medications. Indeed, the target
patient population that stand to benefit from these findings is somewhat different to the
patient groups in our study and previous studies. Furthermore, the study exclusion
criteria, which are common in all studies, are actually a part of the daily anesthesiology
routine.

In conclusion, based on the data collected in this study, we identified a weak correlation
between NRS and ANI values in patients who were not under influence of anesthetic
agents. Although, based on the resources we gathered information before starting this
study as well as our satisfactory personal experience, we believed that ANI monitoring
for anesthetized patients could at least provide alternative data on the present status of
postoperative pain, the data collected in this study did not lead us to any positive
conclusions. In addition, we believe that while ANI values are valuable for anesthetized
patients, they cannot be used for the prediction of postoperative pain severity, contrary to
the findings of other researchers. We should add that more reliable results on this matter
could be obtained through controlled, randomized and prospective studies investigating different anesthesia protocols for operations with longer durations and involving larger patient groups. We also recommend that new researches be carried out to develop an ideal analgesia-monitoring system adjusted for different scenarios in distinct patient groups, such as those at risk of insufficient pain treatment, incommunicable patients, and pediatric, geriatric or non-cooperative patients, who cannot use VAS, NRS or other conventional pain scales.

References


1 Cholecystectomy Using Analgesia Nociception Index (article in Turkish with an abstract in English). Medical Bulletin of Haseki 2016; 54: 212-218


**Table 1** – Demographical findings of all patients and duration of operation

<table>
<thead>
<tr>
<th>Study group</th>
<th>n = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA I / II (n)</td>
<td>17 / 19</td>
</tr>
<tr>
<td>Gender (F/M (n))</td>
<td>21 / 15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.33±12.43</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.22±12.64</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.55±7.72</td>
</tr>
<tr>
<td>BMI</td>
<td>26.21±4.49</td>
</tr>
<tr>
<td>Duration of operation (min) (t&lt;sub&gt;op&lt;/sub&gt;)</td>
<td>68.41±15.81</td>
</tr>
<tr>
<td>NRS* ≤3 / (Group I)</td>
<td>17 (47.22%)</td>
</tr>
<tr>
<td>NRS (4–6) / (Group II)</td>
<td>11 (30.56%)</td>
</tr>
<tr>
<td>NRS ≥7 / (Group III)</td>
<td>8 (22.23%)</td>
</tr>
</tbody>
</table>

ANI: Analgesia Nociception Index;
ASA: American Society of Anesthesiologists
PS: Physical Status
BMI: body mass index
NRS: numerical rating scale.
<table>
<thead>
<tr>
<th></th>
<th>Heart Beat Rate (beats/min)</th>
<th>Systolic Pressure (mmHg)</th>
<th>Diastolic Pressure (mmHg)</th>
<th>ANI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perioperative</strong></td>
<td>65.31±16.76</td>
<td>95.67±15.06</td>
<td>59.72±12.34</td>
<td>70.78±16.66</td>
</tr>
<tr>
<td><strong>Extubation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>70.44±15.42</td>
<td>111.97±18.89</td>
<td>71.44±14.39</td>
<td>59.81±14.46</td>
</tr>
<tr>
<td>After</td>
<td>79.03±14.37</td>
<td>127.14±18.48</td>
<td>75.47±12.16</td>
<td>60.72±14.63</td>
</tr>
</tbody>
</table>

HR\text{periop.}/HR\text{aft.ext} p^1 = 0.006 SAP\text{periop.}/SAP\text{aft.ext} p^2 = 0.0415 DAP\text{peri.op}/DAP\text{aft.ext} p^3 = 0.009

(*) p < 0.05 statistically significant difference
**Table 3** – Comparison of the demographics and other characteristics between patients classified based on pain severity

<table>
<thead>
<tr>
<th>Study group “Pain” level</th>
<th>Group I (NRS ≤ 3)</th>
<th>Group II (NRS = 4-6)</th>
<th>Group III (NRS ≥ 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients / percentage (n / %)</td>
<td>17 (%)</td>
<td>11 (%)</td>
<td>8 (%)</td>
</tr>
<tr>
<td>ASA I / II (n)</td>
<td>5 / 12</td>
<td>9 / 2</td>
<td>3 / 5</td>
</tr>
<tr>
<td>Gender (W/M) (n)</td>
<td>7 / 10</td>
<td>7 / 4</td>
<td>7 / 1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.41±11.53</td>
<td>42.36±8.74</td>
<td>47.87±14.94</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.41±12.12</td>
<td>73.57±11.09</td>
<td>78.21±11.82</td>
</tr>
<tr>
<td>Height (cm) (mean±SD)</td>
<td>168.24±7.44</td>
<td>168.27±7.01</td>
<td>165.13±9.41</td>
</tr>
<tr>
<td>Body Mass Index (BMI) (mean±SD)</td>
<td>26.04±4.09</td>
<td>25.71±2.91</td>
<td>27.34±3.39</td>
</tr>
<tr>
<td>Duration of operation (min) (mean±SD)</td>
<td>67.26±11.56</td>
<td>69.48±14.37</td>
<td>68.45±13.76</td>
</tr>
<tr>
<td>ANI (before extubation) (mean±SD)</td>
<td>58.47±15.32</td>
<td>62.73±15.49</td>
<td>58.50±15.16</td>
</tr>
<tr>
<td>ANI Before Extubation &lt;47 patients</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>ANI (after extubation) (mean±SD)</td>
<td>62.71±15.61</td>
<td>61.73±14.32</td>
<td>55.13±13.54</td>
</tr>
<tr>
<td>ANI Before Extubation &lt;47 patients</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

(*) SD: standard deviation

ANI: Analgesia Nociception Index;
ASA: American Society of Anesthesiologists
PS: Physical Status
BMI: body mass index
NRS: numerical rating scale.
Table 4 – Pre-extubation ANI values of patients classified based on pain level and NRS/ANI correlation

<table>
<thead>
<tr>
<th></th>
<th>Group I - NRS ≤3</th>
<th>Group II - NRS = 4–6</th>
<th>Group III - NRS ≥7</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANI</td>
<td>NRS</td>
<td>ANI</td>
<td>NRS</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>86</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>3</td>
<td>77</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>12</td>
<td>55</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>57</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>54</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>89</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>59</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>44</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>mean±SD</td>
<td>58.47±15.33</td>
<td>62.73±15.49</td>
<td>58.5±15.16</td>
</tr>
<tr>
<td>r</td>
<td>0.016 (weak)</td>
<td>-0.286 (weak)</td>
<td>-0.293 (weak)</td>
</tr>
</tbody>
</table>
r = (0.00–0.29: weak, 0.30–0.49: low, 0.50–0.69: moderate, 0.70–0.89: strong, 0.90–1.00: very strong) relation
Table 5 – Post-extubation ANI values of patients classified based on pain level and NRS/ANI correlation

<table>
<thead>
<tr>
<th></th>
<th>Group I - NRS ≤3</th>
<th>Group II - NRS = 4–6</th>
<th>Group III - NRS ≥7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANI</td>
<td>NRS</td>
<td>ANI</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>2</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>1</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>97</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>2</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>91</td>
<td>2</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>3</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>61</td>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>52</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>71</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>38</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>59</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>71</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>mean±SD</td>
<td>62.71±15.61</td>
<td>61.73±14.32</td>
<td>55.13±13.54</td>
</tr>
<tr>
<td>r</td>
<td>0.135 (weak)</td>
<td>-0.069 (weak)</td>
<td>-0.290 (weak)</td>
</tr>
</tbody>
</table>
r = (0.00–0.29: weak, 0.30–0.49: low, 0.50–0.69: moderate, 0.70–0.89: strong, 0.90–1.00: very strong) relation
Figure – Distribution of ANI and NRS values before and after extubation